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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/718,997
Filing Date: November 21, 2003
Appellant(s): WEI ET AL.

Jason W. Johnston
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed August 26, 2009 appealing from the Office action mailed August 6, 2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

US 7,144,742	BOEHRINGER et al.	12-2006
US 5,573,921	BEHNKE et al.	11-1996
US 2005/0196875	BLATT et al.	9-2005
US 2004/0018637	POLITO et al.	1-2004
US 2003/0162236	HARRIS et al.	8-2003

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 14 – 16 and 29 – 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boehringer et al. (US 7,144,742) in view of Behnke et al. (US 5,573,921).

Boehringer et al. teach a lateral flow (flow-through) assay device for detecting the presence or quantity of an analyte residing in a test sample, said lateral flow assay device comprising a porous membrane in communication with a labeled reagent (optical detection probes) conjugated with a specific binding member, such as a first antibody, specific for the analyte, said porous membrane defining:

a barrier (competitive) zone 16a that can contain either (i) a second antibody immobilized on said porous membrane that can be complexed to an antigen containing a label (optically detectable substance) during use, said antigen being identical to or an analog of the analyte and said label being capable of producing a signal; or (ii) an immobilized analyte analog; and

a detection zone 16b and 16c within which a third antibody is immobilized that is configured to bind to complexes formed between the analyte and said conjugated labeled reagent to produce a first detection signal, said third antibody can also be configured to bind to said antigen or analyte analog from said barrier zone to produce a second detection signal, wherein the amount of analyte within the test sample is determined from said detection signals (see Figure 1; and column 3, lines 14-45; column 5, lines 45-59; column 9, lines 51-67; column 10, lines 1-4 and lines 34-64;

column 11, lines 1-62; column 14, lines 50-65; column 15, lines 10-31; and column 16, lines 10-32).

However, Boehringer et al. fail to teach that the immobilized species, i.e. antibody or analyte analog, in the barrier (competitive) zone comprises a second antibody complexed to the antigen or analyte analog containing an optically detectable substance prior to the application of test sample to the device.

Behnke et al. teach a test strip device for determining the amount of analyte in a sample using immunochemical displacement. The test strip device contains at least one immobilized antibody, wherein the antibody is bound to an analyte analog (tracer) prior to application of test sample to the device. The bound analyte analog (tracer) can also include an attached dye (molecule or particle), such that the area of the test strip comprising the immobilized antibody and tracer can be directly visualized even before beginning the test. A sample containing an analyte of interest is applied to the test strip device, which results in the analyte competing with the bound tracer for binding to the immobilized antibody. As analyte concentration increases, tracer containing the attached dye becomes displaced from the immobilized antibody, and the reduction in the dye previously visualized in the area of immobilized antibody can be utilized to determine the amount of analyte in the sample (see Figures 12a and 12b; column 5, lines 19-67; column 6, lines 1-33 and lines 52-56; column 7, lines 9-27; column 13, lines 51-53).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include with the device of Boehringer et al. the binding

of the antigen or analyte analog containing an optically detectable substance to an immobilized antibody in the barrier zone prior to application of the test sample as taught by Behnke et al. because Behnke et al. teach the benefit of binding an analyte analog attached to a dye to an immobilized antibody on a test strip prior to application of a test sample containing an analyte of interest, wherein the analyte of interest competes for binding with the bound analyte analog, because the bound analyte analog attached to the dye allows for directly visualizing the area of the test strip comprising the immobilized antibody (i.e. barrier zone) even before beginning the test, and also allows for utilizing the reduction in the dye from the area of immobilized antibody after applying the test sample in determining the amount of analyte in the sample.

With respect to Applicant's claims 15 and 16, Boehringer et al. teach that the labels can comprise a visual label, such as a dyed latex bead, or a luminescent compound (see paragraph [0090]).

With respect to Applicant's claims 29 and 30, Boehringer et al. teach that the intensity of the signal at the barrier zone is at its maximum when no analyte is present, and that the conjugated labeled reagent is capable of binding to the antigen within the barrier zone to produce a signal (see column 10, lines 52-67; and column 11, lines 1-44).

With respect to Applicant's claim 31, the device set-up of Boehringer et al., wherein the barrier zone comprises a first antibody for the analyte, the detection zone comprises a second antibody for the analyte/antigen, and the analyte competes for

binding with the labeled antigen in the barrier zone, would allow for the detection signal at the detection zone to reach a maximum value at or near saturation concentration of the analyte within the test sample (see column 10, lines 52-67; and column 11, lines 1-44).

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Boehringer et al. (US 7,144,742) in view of Behnke et al. (US 5,573,921), as applied to claim 14 above, and further in view of Polito et al. (US 2004/0018637).

The Boehringer et al. and Behnke et al. references, which were discussed in the 103(a) rejection above, fail to teach that the labels used for the analyte and antigen (detection probes) emit signals at different wavelengths.

Polito et al. teach a method and apparatus for performing a lateral flow assay. The method utilizes detection agents in the form of particles to label an analyte(s) of interest in order to facilitate detection. Different detection agents can be used with different populations of analytes, wherein the different detection agents can comprise fluorescence agents that fluoresce at different wavelengths. The use of two different detection agents facilitates the detection of two different analytes of interest on the same test strip (see Abstract; and paragraphs [0036]-[0041]).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include with the device of Boehringer et al. and Behnke et al. the use of different labels for the antigen and analyte of interest, wherein the labels fluoresce at different wavelengths as taught by Polito et al. because Polito et al. teach the benefit of utilizing different detection reagents, such as fluorescence agents

that fluoresce at different wavelengths, in order to detect two different analytes of interest, i.e. the analyte and antigen of Boehringer et al., on the same test strip.

Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Boehringer et al. (US 7,144,742) in view of Behnke et al. (US 5,573,921), as applied to claim 14 above, and further in view of Harris et al. (US 2003/0162236).

Boehringer et al. and Behnke et al. also fail to teach the inclusion of a calibration zone that is configured to produced a calibration signal.

Harris et al. teach a method and test strip for measuring the amount of an analyte of interest in a fluid sample, wherein the test strip includes an application point, a contact region, a sample capture zone, and a control capture zone (calibration zone). The contact region contains analyte-binding particles, which bind to and label the analyte of interest. The sample and control capture zones contain immobilized capture reagents specific for the analyte or analyte-binding particles. When the fluid sample is contacted with the test strip, the fluid sample flows through the contact region, wherein any analyte in the sample can bind to the analyte-binding particles. The sample then flows to the sample and control capture zones, wherein a certain amount of analyte-binding particles bind to and are arrested in both the sample and control capture zones. The signals generated in both the sample and control capture zones are determined and compared in order to determine a ratio between 1) the amount of analyte-binding particles arrested in the sample capture zone, and 2) the amount of analyte-binding particles in the control capture zone. This ratio allows for an increased sensitivity and a

more accurate determination of the amount of analyte of interest in a test sample, while also compensating for the variations that result from the dynamic nature of the assays (see paragraphs [0002]-[0007] and [0013]).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include with the device of Boehringer et al. and Behnke et al. a control/calibration zone as taught by Harris et al. because Harris et al. teach the benefit of including a control capture zone that generates a control signal with a test strip in order to determine a ratio that compares the signals generated in a sample capture zone (detection zone) and the control capture zone (calibration/control zone) in order to accurately determine the amount of analyte of interest in a test sample with increased sensitivity, while also compensating for the variations that result from the dynamic nature of the assays.

Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Boehringer et al. (US 7,144,742) in view of Behnke et al. (US 5,573,921), as applied to claim 14 above, and further in view of Blatt et al. (US 2005/0196875).

Boehringer et al. and Behnke et al. fail to teach a specific formula for determining the amount of analyte within the test sample utilizing the signals generated in the various detection/barrier zones.

Blatt et al. teach an assay device for detecting an analyte within a test sample. The assay device can utilize two zones for binding to an analyte or particle-linked antibody (label) and providing a detectable signal in response to the bound

components. The assay quantitation can be determined by reading the signals produced by the two zones, wherein the sample concentration is a result of a calibration algorithm related to the signals produced in the two zones, which provides for a more reliable quantitative analyte concentration result. Further, the summation of the detectable signals from the two zones to produce a substantially constant total signal regardless of analyte concentration provides a reference mechanism for accurate assay performance (see Abstract; and paragraphs [0055]-[0057]).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to create a formula or algorithm that utilizes the signals generated in the detection and/or barrier zones of Boehringer et al. and Behnke et al. as taught by Blatt et al. because Blatt et al. teach the benefit of creating an algorithm related to the signals produced by two zones contained on an assay device in order to quantitatively determine the concentration of an analyte in an applied test sample more reliably, wherein the summation of the detectable signals from the two zones can produce a substantially constant total signal regardless of analyte concentration, which provides a reference mechanism for accurate assay performance.

(10) Response to Argument

Appellant's arguments filed within the Appeal Brief have been fully considered but they are not persuasive. In particular, Appellant argues (see pages 8-10 of Appeal Brief) that independent claim 14 is patentable over Boehringer et al. in view of Behnke et al. because:

(i) The proposed combination fails to teach all of the limitations of independent claim 14, in particular, the limitation requiring an antigen that is “complexed” to the second antibody in the barrier zone prior to application of a test sample to the device;

(ii) One of ordinary skill in the art would not have combined the teachings of Behnke et al. with those of Boehringer et al. because the combination would create a format that would not operate in a manner intended by Boehringer et al; and

(iii) The proposed modification of Boehringer et al. in view of Behnke et al. is based on impermissible hindsight.

However, these arguments are not found persuasive.

(i) With respect to Appellant's first argument that the proposed combination fails to teach all of the limitations of independent claim 14, in particular, the limitation requiring an antigen that is “complexed” to the second antibody in the barrier zone prior to application of a test sample to the device, this argument is not found persuasive because Appellant appears to be arguing against the references individually, and one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The rejection of independent claim 14 is based on an obviousness rejection of Boehringer et al. IN VIEW OF Behnke et al. In order to clearly discuss this 103(a) rejection of independent claim 14, the Boehringer et al. reference must be analyzed carefully. The Boehringer et al. reference teaches a quite similar test device utilizing a

competition-based zone, as recited in the instant application, in order to remedy the "hook effect" that arises with test samples comprising high concentration of target analyte, which also encompasses the goal of the instant application (see column 14, lines 50-65; column 15, lines 6-67; and column 16, lines 1-32). In particular, Boehringer et al. teach a flow-through assay device comprising a porous membrane in communication with a labeled reagent (optical detection probes) conjugated with a specific binding member, such as a first antibody, specific for the analyte (see Figure 1; and column 15, lines 10-16), said porous membrane defining:

a barrier (competitive) zone 16a that can contain either (i) a second antibody immobilized on said porous membrane that can be complexed to an antigen containing a label (optically detectable substance) during use, said antigen being identical to or an analog of the analyte and said label being capable of producing a signal (see Figure 1; column 10, lines 52-64; and column 11, lines 3-25); or (ii) an immobilized analyte analog (see column 14, lines 55-58; and column 15, lines 16-29); and

a detection zone 16b and 16c within which a third antibody is immobilized that is configured to bind to complexes formed between the analyte and said conjugated labeled reagent to produce a first detection signal, said third antibody can also be configured to bind to said antigen or analyte analog from said barrier zone to produce a second detection signal, wherein the amount of analyte within the test sample is determined from said detection signals (see Figure 1; column 3, lines 10-45; column 10, lines 3-60; column 14, lines 50-65; and column 16, lines 10-32).

Thus, Boehringer et al. teach that the barrier (i.e. competitive) zone can comprise either a second antibody (i.e. spb member complementary to the analyte) OR an analyte analog depending on the assay format being used. In the competitive format taught by Boehringer et al., the binding member within the barrier zone comprises an immobilized antibody that binds to a labeled analyte analog that is applied within a labeling zone present on the porous membrane, wherein the labeled analyte analog traverses the porous membrane along with an applied test sample comprising target analyte. In this format, both the target analyte and the applied labeled analyte analog compete for binding to the immobilized antibody within the barrier zone, wherein the capture (i.e. detection) zone also comprises an antibody for the labeled species (see column 9, lines 50-67; column 10, lines 10-67; and column 11, lines 1-62). In a secondary or sandwich format taught by Boehringer et al., the binding member within the barrier zone comprises an immobilized analyte analog and the binding member within the capture zone preferably comprises an antibody that binds to an analyte-labeled reagent complex, wherein the immobilized analyte analog within the barrier zone competes for binding with the target analyte for a labeled specific binding member complementary to the analyte (comparable to Appellant's conjugated detection probes) that is applied to the labeling zone present on the porous membrane (see column 14, lines 50-65; and column 15, lines 10-37).

However, Boehringer et al. fail to specifically teach an embodiment wherein the labeled reagent (i.e. detection probes) comprises a labeled specific binding member complementary to the analyte; the barrier zone comprises an analyte analog containing

a label (i.e. optically detectable substance) that is complexed to an antibody immobilized within the barrier zone prior to application of a test sample; and the capture (i.e. detection) zone comprises another antibody that binds to analyte-labeled reagent complexes. The secondary or sandwich format taught by Boehringer et al. is the closest comparable embodiment to Appellant's independent claim 14, however, all that is needed to remedy this Boehringer et al. embodiment is the use of an antibody to immobilize the analyte analog within the barrier zone, and the inclusion of a label or optically detectable substance to the analyte analog within the barrier zone prior to the application of the test sample.

Therefore, the secondary reference of Behnke et al. was combined with Boehringer et al. in order to remedy these deficiencies, wherein Behnke et al. provide a teaching of and motivation for a competitive binding zone on a test strip device, wherein the binding zone comprises at least one immobilized antibody, wherein the antibody is bound to an analyte analog (tracer) prior to application of test sample to the device. The bound analyte analog (tracer) can also include an attached dye (molecule or particle), such that the area of the test strip comprising the immobilized antibody and tracer can be directly visualized even before beginning the test. A sample containing an analyte of interest is applied to the test strip device, which results in the analyte competing with the bound tracer for binding to the immobilized antibody. As analyte concentration increases, tracer containing the attached dye becomes displaced from the immobilized antibody, and the reduction in the dye previously visualized in the area of immobilized antibody can be utilized to determine the amount of analyte in the sample

(see Figures 12a and 12b; column 5, lines 19-67; column 6, lines 1-33 and lines 52-56; column 7, lines 9-27; column 13, lines 51-53).

Therefore, it was determined to be obvious to one of ordinary skill in the art at the time of the invention to include with the device of Boehringer et al. the binding (i.e. complexing) of the antigen or analyte analog containing an optically detectable substance to an immobilized antibody in the barrier zone prior to application of the test sample as taught by Behnke et al. because Behnke et al. teach the benefit of binding an analyte analog attached to a dye to an immobilized antibody on a test strip prior to application of a test sample containing an analyte of interest, wherein the analyte of interest competes for binding with the bound analyte analog, because the bound analyte analog attached to the dye allows for directly visualizing the area of the test strip comprising the immobilized antibody (i.e. barrier zone) even before beginning the test, and also allows for utilizing the reduction in the dye from the area of immobilized antibody after applying the test sample in determining the amount of analyte in the sample.

Thus, it is not considered persuasive that the combination of Boehringer et al. in view of Behnke et al. fails to teach limitations recited in independent claim 14 because this combination would result in the flow-through assay device taught by Boehringer et al., which contains the recited labeled reagent (i.e. optical detection probes), the barrier (i.e. competitive) zone comprising an immobilized analyte analog, and the capture (i.e. detection) zone within which an antibody is immobilized that is configured to bind to complexes formed between the analyte and the labeled reagent, further containing an

antibody immobilized within the barrier zone for complexing the analyte analog and attaching an optically detectable substance or dye to the analyte analog prior to sample application as taught by Behnke et al. In conclusion, this combination would in fact contain all of the limitations required by Appellant's claim 14.

(ii) With respect to Appellant's second argument that one of ordinary skill in the art would not have combined the teachings of Behnke et al. with those of Boehringer et al. because the combination would create a format that would not operate in a manner intended by Boehringer et al, this argument is not found persuasive because Appellant is only focusing on the competitive format taught by Boehringer et al. and not the device created by the combination of Boehringer et al. in view of Behnke et al.

The device created by this combination, which is discussed in the arguments directly above, would result in the barrier zone of Boehringer et al. still containing the immobilized analyte analog. However, the only change is that the analyte analog is complexed or immobilized through the use of an antibody as taught by Behnke et al. and the immobilized analyte analog further contains an optically detectable substance or dye as taught by Behnke et al. prior to application of a test sample. The reasons and motivation for this combination were already discussed above, and are considered applicable to Appellant's arguments here.

Further, this modification to the device of Boehringer et al. would still function properly and would perform its intended function if the analyte analog is bound to an antibody immobilized within the barrier zone, because the function of the barrier zone is

to compete for binding with the analyte and/or labeled reagent, and this would occur either way. In addition, Appellant has not provided any support or evidence for the reason WHY the device of Boehringer et al. would not operate in the manner intended by Boehringer et al. if the device was combined with Behnke et al. Thus, this argument is also not found persuasive.

(iii) With respect to Appellant's third argument regarding impermissible hindsight, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Therefore, when considering the teachings of the prior art references, and the reasons and motivation for the combination discussed in the arguments above, it is not considered persuasive that the modification of Boehringer et al. in view of Behnke et al. is based on impermissible hindsight.

With respect to Appellant's arguments (see pages 11-12 of Appeal Brief) over the dependent claims, the combination of Boehringer et al. in view of Behnke et al. is considered to teach all of the limitations recited in Appellant's independent claim 14, as discussed above. Further, Appellant is limiting their arguments to only the competitive

format taught by Boehringer et al. and therefore, is not considering the reference as a whole, or in its combination with Behnke et al.

Finally, with respect to Appellant's last argument (see pages 12-19 of Appeal Brief) over the Blatt et al. reference (US 2005/0196875), as discussed in the 103(a) rejection above, Blatt et al. teach the benefit of creating an algorithm related to signals produced by two zones contained on an assay device in order to quantitatively determine the concentration of an analyte in an applied test sample more reliably, wherein the summation of the detectable signals from the two zones can produce a substantially constant total signal regardless of analyte concentration, which provides a reference mechanism for accurate assay performance (see Abstract; and paragraphs [0055]-[0057]). It is considered irrelevant that Blatt et al. only teach a single labeled indicator and not a second signal-producing substance, because this limitation is met by the primary references of Boehringer et al. in view of Behnke. What is relevant is the fact that Blatt et al. teach the creation of an algorithm using two signals created by two different zones on an assay device. Because the combination of Boehringer et al. in view Behnke results in this type of assay device, wherein two zones and two signals are created, the combination of Boehringer et al. in view of Behnke and Blatt et al. does in fact read on Appellant's formulae recited in claim 19. Again, it appears that Appellant is arguing against the references individually, and one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of

references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Jacqueline DiRamio/
Examiner, Art Unit 1641

Conferees:

/Mark L. Shibuya/
Supervisory Patent Examiner, Art Unit 1641

/Larry R. Helms/

Supervisory Patent Examiner, Art Unit 1643